

**REMARKS**

I. **Status of the Claims**

Claims 1-77 are currently pending, with claims 1 (in part), 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65, 67 and 69-77 withdrawn from consideration as directed to a non-elected invention. Upon entry of this amendment, claims 25-28 and 48 are amended without prejudice or disclaimer. These amendments are formal in nature and simply conform the language in these dependent claims with the language in independent claim 1.

II. **Claim Rejections under 35 U.S.C. §112**

A. **Written Description**

Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph for allegedly failing to describe the invention such that one of ordinary skill could determine that the inventors had possession of the claimed invention at the time the application was filed. The overarching concern expressed in the Office Action is that the specification allegedly fails to provide a “‘precise definition, such as by structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials” (paragraph bridging pages 4 and 5 of the Office Action). According to the Office Action, this alleged deficiency is compounded by two additional shortcomings of the specification, namely the alleged failure to provide guidance with respect to: 1) what specific carrier-type transport proteins can successfully be utilized, which is considered problematic in view of the Examiner’s belief that only carrier-type transport proteins with wide substrate specificity can be used in the claimed methods, and 2) the type of reporters that would not interfere with the transport process. These general and specific concerns are addressed in turn below.

The central issue with respect to this written description rejection, is what the appropriate standard is for assessing whether the written description requirement has been satisfied. As pointed out in the last response, the initial inquiry must be to ascertain what the “claimed invention is.” This is the case because the general standard for determining whether the written

description requirement has been satisfied involves determining whether the specification describes *the claimed invention* in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the *claimed invention* (see, e.g., MPEP 2163; and *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116). Here, the claims clearly state that the invention is directed to screening methods. The inquiry with respect to the current claims thus becomes what the appropriate standard is for determining whether a screening method has been adequately described.

The Office takes the position that since the claims involve chemical species that the specification must therefore provide a precise definition of the chemical species referred to in the claims, by structure, formula or chemical name. As pointed out in the last response, Applicants submit that the standard adopted by the Office, although perhaps appropriate for claims directed to a chemical compound *per se*, is inappropriate for screening methods.

The Office dismisses this argument, citing *University of Rochester v. G.D. Searle & Co., Inc.* [358 F.3d 916 (Fed. Cir. 2004)] (the “Rochester case”) for the proposition that method claims involving the use of a chemical compound must describe the chemical compounds in sufficient detail such that infringing compounds can be distinguished from non-infringing compounds. This view of the Rochester case misses a distinction the Federal Circuit made between methods of using a chemical compound (e.g., in treatment methods) and methods of screening for a chemical compound having a desired activity.

The general issue in the Rochester case was whether the specification provided adequate written description for the therapeutic method claims that issued in U.S. Patent 6,048,850. The claims in the '850 patent were directed to methods of selectively inhibiting an enzyme called prostaglandin H synthase-2 (PGHS-2) by administering a non-steroidal compound. The specific issue was whether these therapeutic method claims had been adequately described given that the specification was found to neither disclose a non-steroidal compound that could work or how to obtain such a compound. The Federal Circuit held that the method of treatment claims were invalid because the specification did not disclose "just which 'peptides, polynucleotides, and small organic molecules' have the desired characteristic." (*University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927 (Fed. Cir. 2004)). The Federal Circuit agreed with the

district court that "[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method." *Id.* at 926.

But the Federal Circuit went on to note that the parent of the '850 patent had issued as U.S. Patent 5,837,479 with claims directed to "methods for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2", i.e., with screening claims. Although the Federal Circuit concluded that the '850 patent did not adequately describe method of treatment claims, it nonetheless noted that the assays for screening compounds "appeared to be supported by the specification . . . but those claims are already issued in the '479 patent." *Id.* at 928. So the Rochester case suggests that although a description of a specific compound may be required to satisfy the written description requirement for claims directed to methods of treatment, that it is not necessary to adequately describe a screening method. If the Office is inclined to continue to rely on the Rochester decision in making its written description rejection, Applicants request that the Office point out what section of the case supports the view that chemical structures must be provided in the specification to provide written description support for a screening claim.

The extent to which the '479 patent describes the type of compounds to be screened supports this conclusion. Applicants invite the Examiner to review sections 5.6 and 5.7 (column 25, line 30 to column 28 line 35) of the enclosed copy of the '479 patent. In describing the type of compounds that could be screened, the '479 patent simply states that the compounds "include but are not limited to nucleic acids encoding PGHS-2 and homologues, analogues, and deletions thereof, as well as antisense, ribozyme, triple helix, antibody, and polypeptide molecules and small inorganic molecules." Although this is a very general description, and provides much less detail than Applicants have included in the specification with respect to the nature of the complexes that can be screened, the Federal Circuit nonetheless suggested in the Rochester decision that the screening claims in the '479 appeared to be supported.

The key issue is whether a method can be practiced without knowledge of a compound that has the desired activity. Although the identity of a compound may be required to practice a method of treating a particular disease, the identity of a compound is not required to practice a

screening method. Indeed, as pointed out in the last response, the purpose of a screening method is to take a population of compounds in which the identity of the members is typically unknown and identify from the population one or more compounds with the desired activity.

For all these reasons, Applicants reiterate their position made in the last response, namely that the Office is applying an inappropriate standard for the currently claimed screening methods by requiring that the specification provide specific chemical details (e.g., structure, formula or chemical name) regarding the nature of the compounds and transport proteins that are used in the method. But in any event, as described in the last response, the specification does in fact provide an extensive list of representative species of compounds, reporters, and carrier-type transport proteins. Thus, one of ordinary skill in the art could readily conclude that Applicants were in possession of the presently claimed invention, thereby satisfying the written description requirement.

Although the foregoing reasons are deemed sufficient in themselves to fully address this rejection, Applicants nonetheless address the specific issues raised in the Office Action, which are alleged to demonstrate that the specification fails to adequately describe the current claims. As noted above, one issue is the assertion in the Office Action that "not all carrier-type transport proteins can be used for screening because they do not possess the requisite "wide substrate specificity" that the Office Action says is critical to the claimed methods. Applicants initially note that nowhere in the specification or prosecution history have Applicants stated that the claimed methods will only work with carrier-type transport proteins that have "wide substrate specificity." The claimed methods in fact can be performed even with carrier-type transport proteins that have relatively narrow substrate specificities.

The underlying concern with respect to this particular issue appears to be the view that many of the compounds tested will turn out not to be substrates for carrier-type transport proteins having narrow substrate specificities. Applicants submit that this concern is unwarranted on several grounds. First, it may well be the case that a smaller percentage of compounds will be identified as active during screening methods conducted with a carrier-protein having relatively narrow substrate specificity requirements as compared to a transporter with wide substrate specificity. But it does not follow that simply because many complexes may not be transported

that these transport proteins cannot be used and that the claimed methods are thus inadequately described. Those in the art recognize that in screening methods the vast majority of compounds will not work; this is simply accepted as an inherent aspect of screening methods. Secondly, the general substrate specificity requirements of a number of carrier-type transport proteins were known as of the priority date of this application. Thus, one of ordinary skill in the art would have known what general classes of compounds had an increased likelihood of being successful in the screening methods, and thus could adjust the starting composition of the library to be screened accordingly. Third, although the Examiner appears to be of the view that there are only a very limited number of carrier type transport proteins that have what the Office terms "wide substrate specificity," this is not the case. There are in fact a number of different classes of carrier-type transport proteins that have relatively broad substrate specificity. The enclosed declaration from Dr. William Dower, the lead inventor for this case, and accompanying scientific articles, for instance, demonstrate this. These articles also support the second point made above, namely that those of ordinary skill in the art recognized the general substrate requirements of carrier-type transport proteins as of the priority date of this application. Finally, it should be recognized that even complexes that are not transported are not "failures," since the structural and chemical characteristics of complexes that are not transported provide useful information in further understanding the substrate requirements of the carrier-type transport protein.

The other specific issue raised in the Office Action concerns the assertion that the specification fails to provide adequate guidance regarding which reporters will work and which will interfere with transport mechanism of the carrier-type transport protein. As an initial matter, it is reiterated that the specification provides guidance regarding different types of reporters that can be utilized including reporters that are substrates for intracellular enzymes, masked reporters, reporters that interact with intracellular agents, internally quenched reporters and various bioactive reporters (see, e.g., pages 32-36 and examples 5-8). Additional specific reporters are listed, for example, at page 19, lines 7-11. Furthermore, as already described above, those in the art were aware of the general structural and chemical requirements of many carrier-type transport proteins as of the priority date of this application. This knowledge could have been used to inform the selection of appropriate reporters as of the priority date of this application. Finally, to

the extent that the nature of the reporter was critical with respect to a particular carrier-type transport protein (e.g., one with strict substrate requirements), a preferred reporter could readily be identified simply by taking a known substrate and then conducting a screening method as described in the specification with varying reporters to identify ones that did not interfere with transport. This is addressed further in the enclosed declaration from Dr. Dower.

For all the foregoing reasons, it is submitted that the specification does adequately describe the claims across their entire scope. Accordingly, it is requested that this ground of rejection be withdrawn.

B. Enablement

Claims 1-3, 14-16, 25-35, 37, 40, 46-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph as allegedly not being enabled by the specification. Although the specification is said to be enabling for screening a library of dipeptides for a PEPT1 dipeptide transporter and a library of glycholic acid derivatives for the ASBT ileal bile acid transporter, the Office Action concludes that the specification does not enable the claims across their entire breadth. The Office Action reemphasizes the same two factors raised in the written description rejection to justify this conclusion, namely that: 1) there is no guidance provided in the specification to distinguish between carrier-type transport proteins that have sufficiently wide substrate specificity to work in the assay and those transport proteins with narrow substrate specificity that the Office alleges will not work in the assay, and 2) there is no guidance in the specification regarding how to distinguish between reporters that do not interfere with transport and those that do. These two issues are addressed in turn.

With respect to the first issue, Applicants reiterate that there is no basis for concluding that the claimed methods will not work with carrier-type transport proteins that have relatively narrow substrate specificities. As noted earlier, although a smaller percentage of complexes in a library may be transported by a carrier-type transport protein with narrow substrate specificity as compared to one with broad specificity, it does not follow that the methods are thus not enabled. The *In re Wands* decision cited by the Examiner illustrates this point.

The issue in *Wands* was whether the specification of the *Wands* patent enabled production of a class of antibodies having IgM isotype and a binding affinity of at least  $10^9 \text{ M}^{-1}$  using Kohler Milstein technology. As the Examiner is aware, Kohler Milstein technology is a classical technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired characteristics. The evidence indicated that only a very small percentage of the hybridomas to be screened would produce antibodies having the desired property. Nevertheless, the court found that “practitioners of this art are prepared *to screen negative hybridomas in order to find one that makes the desired antibody*” (858 F.2d at 740, emphasis supplied). The *Wands* patent was held to be enabled.

Moreover, as indicated above and in the enclosed declaration from Dr. Dower, the general substrate requirements for a number of carrier-type transport proteins was known as of the priority date of this application. This knowledge could be used to inform the decision of what types of libraries to screen, thereby increasing the likelihood of successfully identifying compounds.

The second major enablement issue raised in the Office Action is that the specification allegedly does not provide guidance on how to select a reporter that will not interfere with the transport process. As just indicated, however, there was a general understanding in the art regarding the substrate requirements for a number of carrier-type transport proteins as of the priority date of this application that one of ordinary skill in the art could draw upon in selecting reporters that had an increased likelihood of being useful. Moreover, as noted above, if it was found that a particular carrier-type transporter had little tolerance with respect to the nature of the reporter, a preliminary screen could be performed to identify an appropriate reporter. Such a screen would not constitute undue experimentation because it could be routinely conducted in view of the disclosure in the specification and methods known in the art.

So for all the foregoing reasons, it is submitted that the claims are fully enabled. Accordingly, it is requested that the rejection be withdrawn.

IV. Claim Rejections under 35 U.S.C. §102

A. Abe Distinguished

Claims 1, 2, 35, 37, 56, 58, 66 and 68 are said to be anticipated by Abe et al. (Abe, H. (1998) Bioconjugate Chem. 10:24-31). The Office says that Abe discusses methods of screening certain fluorescently or radioactively labeled dipeptides or analogs against PEPT1, a dipeptide carrier-type transport protein. The compounds labeled with fluorescein isothiocyanate are said to preferentially generate a signal as compared to the corresponding compounds labeled with a coumarin dye because the coumarin-labeled compounds are quickly degraded inside the cells.

In response, it is submitted that Abe does not teach or suggest a method involving "detecting a signal from the reporter of a *complex while internalized within a cell.*" Said differently, Abe does not teach or suggest a method in which the signal is detected while the complex is internalized within the cell. Instead, Abe discusses a method in which detection of a signal associated with an internalized dipeptide analog does not take place until after the analog has been extracted from the cells, and thus detection does not occur while the complex is internalized within the cell as required by the currently pending claims.

More specifically, the methods discussed in Abe involve: 1) incubation of the cells with a solution containing a fluorescent dipeptide analog, 2) removal of the incubation solution by aspiration, 3) lysis of the cells to form a cellular extract, 4) centrifugation of the extract to remove cellular debris and collection of the supernatant, and 5) measurement of fluorescence intensity of a diluted solution of the supernatant (Abe, page 27, column 1, section entitled "Uptake Experiments in Monolayer Caco-2 Cells"). The currently claimed methods involve a much simpler process in which signal is detected of a "complex internalized within a cell."

B. Swaan Distinguished

Claims 1-3, 14, 35, 56 and 66 are said to be anticipated by Swaan et al. (Swann, P.W., et al. (1997) Bioconjugate Chem. 8:520-525; "Swaan"). The Office Action says that Swaan discusses screening radiolabeled bile acid-peptide conjugates against a bile acid transporter. In the system discussed by Swaan, the Office Action correlates the various elements of the claims with the features of the Swaan method as follows: 1) "compounds" = various dipeptides, 2) "reporter" = radiolabeled bile acid, 3) "population of cells" = CaCo-2 cells, and 3) "signal" =

radioactivity. Swaan is also said to discuss methods in which the transport and metabolism of the radiolabeled bile acid-peptide conjugate, ChEASASA, was monitored and found to be enzymatically cleaved to radiolabeled cholic acid. In this method, the radiolabeled cholic acid signal is said to be preferentially generated only when internalized in the cell, thus satisfying the requirement in the claims for preferential generation of a signal once the reporter is internalized.

But Swaan suffers from the same deficiency as Abe. It too does not teach or suggest a method involving “detecting a signal from the reporter of a *complex while internalized within a cell.*” Instead, detection of signal occurs when the reporter is *outside* the cell. In the methods discussed by Swaan, radiolabeled substrates are incubated on the apical side of cell monolayers and then samples taken from the basolateral side of the cell monolayer (i.e., on the *external* side of the cell monolayer opposite the apical side) at different time points. The amount of radioactivity in the samples taken from the basolateral side is then measured to determine the extent of transport.

Because both Abe and Swaan do not teach or suggest each and every element of the currently claimed invention as required to establish anticipation, it is requested that these anticipation rejections be withdrawn.

V. Claim Rejections under 35 U.S.C. §103

Claims 1-3, 14, 35, 56, 66 and 68 are rejected as obvious over Swaan in view of Dawson et al. (U.S. Patent No. 5,589,358). Swaan is cited for the reasons discussed above. Dawson is said to discuss the use of control assays.

This combination of these two references, however, fails to render the rejected claims obvious, because Dawson fails to remedy the deficiencies of Swaan that were listed in the previous section. Because the cited references, even when combined, do not teach or suggest each and every element of the pending claims as required to establish a *prima facie* case of obviousness, it is requested that this rejection be withdrawn.

Appl. No. 09/661,927  
Amdt. dated August 23, 2004  
Amendment under 37 CFR 1.116 Expedited Procedure Examining Group

PATENT

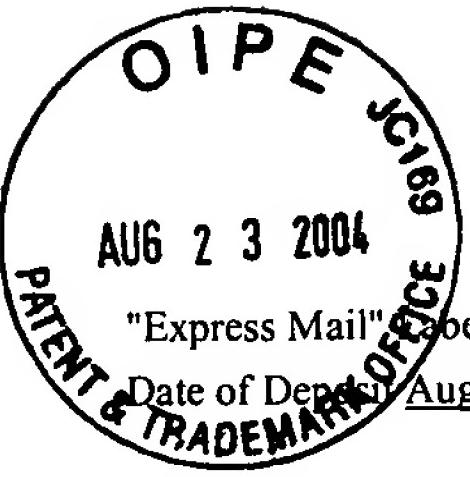
If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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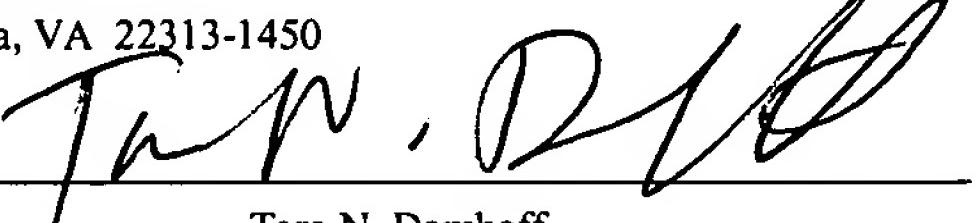
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

William J. Dower, et al.

Application No.: 09/661,927

Filed: September 14, 2000

For: SUBSTRATES AND SCREENING METHODS FOR TRANSPORT PROTEINS

Examiner: Epperson, Jon D.

Art Unit: 1639

### DECLARATION UNDER 37 C.F.R. §1.132

**Mail Stop RCE**  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, William J. Dower, hereby declare as follows:

(1) I received a Ph.D. in Biological Sciences from the University of California at San Diego, and I performed post-doctoral work at Stanford University in the field of cell and molecular biology. From 1984 to 1989, I was a research scientist at BioRad Laboratories, last holding the position of Senior Research Biochemist. From 1989 to 1999, I was a research scientist at Affymax Research Institute, eventually assuming the position of Senior Director of Molecular Biology. Since 1999, I have been employed by XenoPort, Inc., the owner of the above-identified patent application, where I currently

hold the position of Vice President, Discovery Biology. I am also a co-inventor of the instant patent application.

(2) I have read the above-captioned application and followed the prosecution thereof, including the Office Action mailed March 23, 2004.

(3) I understand that the Examiner has questioned whether a reasonable number of carrier-type transport proteins have sufficiently wide substrate specificity to be used in the presently claimed methods.

The Examiner may have the view that carrier-type transport proteins have specific substrate requirements because the initial reports on transporters sometimes refer to a single or limited number of substrates. Subsequent investigations, however, typically demonstrate that carrier-type transporters can transport various other compounds, although, as indicated above, some have greater substrate specificity than others.

The solute carrier (SLC) superfamily of proteins for example, which are carrier-type transport proteins, consists of more than forty families, many of which have a diversity of members. Typically, the members of each family, as a group, recognize many substrates; and in some cases, individual transporters recognize a large number of natural substrates, such as nutrients required by the transporter-expressing cells. The peptide transporter, for example, transports many of the di- and tri-peptides derived from genetically-encoded proteins (hundreds to thousands of compounds). In addition, many of the individual members of most SLC families recognize more (often many more) compounds as substrates than the set of compounds initially identified as the natural substrates of the transporter. An excellent example of a class of transporters with broad substrate specificity is the organic ion transporters. There are dozens of these transporters in several SLC families. These include organic anion transporters (OATs), organic anion transport polypeptides (OATPs), organic cation transporters (OCTs), monocarboxylate transporters (MCTs), the multivitamin/sugar transporters (SMVTs,

SVCTs, SGLTs), Bile acid transporters (e.g., LBAT), and the like. The great majority of transporters in these groups each recognize a diverse array of tens to hundreds of different compounds. In many cases – particularly the OATs, OCTs, and OATPs – individual transporters may recognize hundreds to many hundreds of compounds as substrates. Among the many amino acid transporters, most also recognize tens of natural substrates, as well as many additional synthetic compounds.

The following review articles (copies enclosed), which cite a number of references that predate the priority date of the instant application, describe the relatively broad substrate specificity of many carrier-type transport proteins:

(a) Steffansen, B. et al. (2003) Eur. J. of Pharmaceutical Sciences 21:3-16; and Yang, C. et al. (2001) Exp. Opin. Biol. Ther. 1:159-175 are general review articles that discuss the range of substrate specificities of a large number of carrier-type transport proteins (e.g., amino acid transporters, peptide carriers, glucose carriers, fatty acid transporters, nucleoside transporters, monocarboxylate transporters, phosphate transporters, bile acid transporters, organic anion transporters, organic cation transporters and vitamin transporters);

(b) Hagenbuch, B. and Meier, P.J. (2003) Biochimica et Biophysica Acta 1609:1-18; Kim, R.B. (2003) Eur. J. Clin. Invest. 33 (Suppl. 2):1-5); van Montfoort, J.E., et al. (2003) Current Drug Metabolism 4:185-211 specifically review the diverse substrate specificities of organic anion transporters;

(c) Uchino, H. et al. (2002) Molecular Pharmacology 61:729-737 focuses on the substrate specificity of amino acid transporters; and

(d) Tamai, I., et al. (1995) Biochem. Biophys. Res. Commun. 214:482-489 specifically reviews the substrate specificity of monocarboxylic acid transporters.

Thus, in my opinion, the literature supports the view that carrier-type transport proteins have a sufficiently broad range of substrate specificities such that they can generally be used in the currently claimed methods. Although some carrier-type transport proteins have narrower substrate specificities than others and are thus expected to transport fewer complexes than carrier-type transport proteins with broader specificity,

such carrier-type transport proteins still have sufficiently broad specificity so they can be used in the currently claimed methods.

(4) I also understand that the Examiner questions whether one of ordinary skill in the art could identify a reporter that did not interfere with the transport process in the presently claimed methods without undue experimentation. It is my opinion that one of ordinary skill could identify suitable reporters without undue experimentation. One of ordinary skill, for instance, would recognize that a pre-screen analogous to current methods could be conducted using a known substrate(s) for a transporter to which various reporters are conjugated and then tested to identify those compatible with transport. Using just such an approach, the NBD reporter described in Example 4, the first reporter we tested, was found to be compatible with transport by PEPT-1, and thus suitable as a reporter in a screening format. Moreover, the selection of a reporter by one of ordinary skill in the art would be informed by the considerable knowledge in the art regarding the substrate specificities of the various carrier-type transport proteins (see, e.g., the references listed in paragraph (2)).

I thus conclude that the skilled practitioner could readily identify suitable reporters for a given transporter based on the knowledge known in the art regarding substrate specificities and/or using the prescreening approach just described.

(5) Finally, I understand that the Examiner considers the Abe reference (Abe, H., et al. (1998) Bioconjugate Chem. 10:24-31) to raise technical concerns about performing methods such as currently claimed.

I understand, for example, that the Examiner questions whether the passive uptake discussed in Abe makes it difficult to distinguish between passive uptake and transport due to the activity of the transporter. In my opinion, one of ordinary skill would have readily recognized what controls to use to distinguish between these two forms of uptake. One approach typically used in screening transporters, for instance, is to conduct the screening process with control cells that do not express the transport protein. The

'difference in the uptake of a test compound between cells expressing the transporter and cells not expressing the transporter indicates the active transport of the test compound attributable to the transporter under study. Another common approach is to add a known substrate to the cells to determine if it inhibits uptake. Uptake of the test compound inhibited by excess of known substrate is taken as the "specific" transport attributable to the activity of transporter on the test compound. The absence of inhibition indicates the test compound is taken into the cells by a mechanism other than the transporter under study, including via passive diffusion. Both the cited Abe reference and the cited Swaan reference (Swaan, P.W., et al. (1997) Bioconjugate Chem. 8:520-525) discuss related approaches for distinguishing between passive uptake and uptake due to activity of the transporter (see, e.g., Abe at p.29, col. 1, section entitled "Accumulation of Fluorescent Dipeptide Analogues by Caco-2 Cells" and Swaan at p. 524, column 2, first full paragraph).

I also understand that the Examiner questions whether the apparent failure of the complexes described in Abe to be transported by PEPT1 raises questions regarding the ability to use the presently claimed methods, specifically whether this apparent failure supports the view that reporters may prevent uptake of complexes by transporters. In my opinion, there are at least two reasons why Abe fails to support this conclusion.

First, it is important to recognize that some compounds possess physical chemical properties that impart an intrinsically high level of passive uptake. High levels of passive uptake can result in a high background against which the transporter-dependent (or active) uptake is measured. In some cases the background is too high, relative to an active transport component, to allow reliable detection of the active component. It is my opinion that the complexes discussed in Abe may well have been substrates for PEPT1, but that the high passive uptake of these particular compounds prevented the detection of active transport. It is a well known and accepted feature of high throughput screens, however, that some of the compounds will simply be missed by the screening method.

Second, screens such as described in Example 4 have been successfully conducted with the same transporter used by Abe (i.e., PEPT1), thus illustrating that a reporter can be used to detect uptake into cells via the action of a transporter such as used by Abe.

I thus conclude that Abe does not support the view that performing the currently claimed methods is unpredictable.

(6) I further declare that all statements made herein of my own knowledge are true and that statements made of information and belief are believed to be true. I further acknowledge that any willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and may jeopardize the validity of the application or any patent issuing therefrom.



\_\_\_\_\_  
William J. Dower

Date: 8/20/04